Original Article

Neonatal seizures – Levetiracetam versus phenobarbital

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ABSTRACT

Background: Neonatal seizures (NS) are an important cause of admission in the neonatal intensive care units (NICU) in India. While the drug which stood the test of time is phenobarbitone (PB), levetiracetam (LEV) may be a better alternative with superior effects. **Objective:** The objective of the study was to compare the efficacy of LEV and PB for the treatment and follow-up of term neonates with NS. **Materials and Methods:** This open-labeled randomized controlled trial was carried out on 80 newborn babies suffering from clinically apparent seizures who were admitted in a tertiary care NICU of Bihar. All admitted term neonates who were without transient metabolic disorders (hypoglycemia or hypocalcemia) were randomly assigned. LEV (n=42) at an intravenous (IV) doses of 10 mg/kg was gradually increased to 15 mg/kg and PB (n=38) at a dose of 20 mg/kg/dose IV over 20 min gradually increased in aliquots of 10 mg/kg up to 40 mg/kg total dose. Neonates whose seizures were not controlled by the assigned drug were then crossed over to be treated with the other drug in same dose. **Results:** Clinical features and baseline characteristics were compared in both groups. Seizures were controlled in 66.6% neonates who received LEV, as compared to 81.5% neonates who received PB ($p>0.05$). Short-term adverse effects (cardiorespiratory depression and sedation) were noted in 52.6% babies in PB group in comparison to 7.1% babies in LEV group ($p<0.05$). Long-term neuromotor and developmental complications were less in LEV group as compared to PB group ($p<0.05$) at 1 year of age. **Conclusion:** LEV and PB, both were equally effective in control of clinical seizures irrespective of the etiology, but LEV is superior in terms of short- and long-term neurodevelopmental outcomes than PB.

Key words: *Levetiracetam, Neonatal seizure, Outcome, Phenobarbital*

Neonatal seizures (NS) are the most frequent clinical manifestation of the central nervous system dysfunction in the newborn. Its prevalence is approximately 1.5%, and overall incidence approximately 3/1000 live births. The incidence of pre-term infants is very high (57–132/1000 live births). Most (80%) of the NSs occur in the first 1–2 days to the 1st week of life [1]. NS have deleterious effects on the developing brain, so their prompt recognition and treatment are crucial to prevent future complications. The most common causes of seizures in the neonatal period are hypoxic-ischemic encephalopathy (HIE), central nervous system infections, cerebral infarctions, intracranial hemorrhage, and metabolic abnormalities.

There are currently no evidence-based guidelines for the evaluation and management of NS. Phenobarbitone (PB) is considered as the first-line treatment for NS [2]. Yet, a recent Cochrane review concluded that there was little evidence from randomized controlled trials to support the use of any of the anticonvulsants currently used in the neonatal period [3]. Conventional treatment (PB and phenytoin) only achieves clinical control in 50–80% of cases and is even less effective in controlling most neonatal electroencephalographic seizures [4]. However, there is increasing concern over the long-term adverse effects of PB, since it was shown to increase neuronal apoptosis in animal models [5] and induces cognitive impairment in infants and toddlers [6].

Levetiracetam (LEV) is an effective and well-tolerated antiepileptic drug currently licensed for the treatment of NS. There are hardly any reports of severe, life-threatening side effects, while most frequently observed adverse effects included somnolence and behavioral problems [7]. Furthermore, LEV presents a favorable profile regarding neuronal apoptosis: In contrast to most other established anti-epileptic drugs, it was not found to increase apoptosis in the developing rodent brain [8] and does not interfere with neuroprotective upregulation of hypoxia-inducible factor 1 [9] and decreases neurodegeneration in rodent models of hypoxia/ischemia [10] or epilepsy [11,12]. This study was done to compare efficacy of LEV and PB in the treatment of clinically apparent seizures in term neonates and their outcome on follow-up at 1 year of age.

MATERIALS AND METHODS

This was an open-label randomized controlled study. This study included 80 neonates (57 males and 23 females) admitted

in neonatal intensive care unit (NICU) of the department of pediatrics of a tertiary hospital in Bihar suffering from clinically apparent seizure during the period from April 2018 to September 2019. The present study was conducted in accordance with the current version of the Declaration of Helsinki. Informed written consents were taken from guardian/parents of children involved.

Block randomization of 80 numbers in blocks of four was done using computer generated random numbers. They were put in serially numbered opaque envelopes and sealed. This was done by a person not involved in study. These pre-numbered sealed envelopes were opened to determine the anticonvulsant to be given to the baby. Our trial was an open-label trial, so the doctors and nursing staff were aware of the treatment assignments. However, the electroencephalography (EEG) technicians and neurologist reporting the EEG were blinded to the intervention.

The inclusion criteria were all term neonates (≥37 weeks of gestation) admitted with clinically apparent seizures after ruling out hypoglycemia, hypocalcemia, and other metabolic disorders. Clinical criteria for the diagnosis of NS were subtle seizures and spontaneous paroxysmal, repetitive motor or autonomic phenomena such as lip-smacking, chewing, paddling, cyclic movements, or respiratory irregularities. Neonates with clonic movement, which could be unifocal, multifocal or generalized, and tonic posturing with or without abnormal gaze were included in the study. The exclusion criteria were neonates with seizure responding to correction of hypoglycemia, hypocalcemia, or any other metabolic disorder. Preterm neonates (≤36 weeks 6 days of gestation), neonates with the major congenital malformation or myoclonic jerks, and neonates who were intubated at admission to NICU were also excluded from the study.

Patient details (name, age, sex, weight, head circumference, and length) were recorded on a pre-structured pro forma. Patency of airway, breathing, and circulation was ensured based on standard guidelines [13]. After a cannula was secured, blood sugar, serum calcium, and blood for other tests were drawn. Hypoglycemia was defined as blood sugar <45 mg/dl [13]. Hypocalcemia was defined as ionized calcium <4.8 mg/dl (1.2 mmol/l) in term neonates [14]. If seizures persisted even after correction of hypoglycemia and hypocalcemia, babies were randomized to either LEV (Group A) or PB (Group B).

In Group A, baby was loaded with initial intravenous (IV) doses of 10 mg/kg LEV. If seizures persisted, an additional aliquot of 5 mg/kg was given to a total of 15 mg/kg of LEV. The maintenance therapy was continued every 12 h at the dose at which seizures were controlled. Cardiac rate, rhythm, and blood pressure were monitored during the infusion. If seizure persisted, the babies were crossed over to IV PB. In Group B, babies were loaded with injection PB at 20 mg/kg slow IV infusion over 30 min under cardiorespiratory monitoring. If seizure persisted, baby was reloaded with 10 mg/kg aliquots each to a maximum total dose of 40 mg/kg. The maintenance therapy was started after 24 h of loading of PB. If seizures persisted, baby was crossed over to receive IV LEV.

If seizure persisted after two drugs, and then a third-line drug-like midazolam was used IV at 0.2 mg/kg/dose followed by continuous infusion. Administration of the drug was discontinued if respiratory depression (cessation of respiration for >20 s, or <20 s associated with cyanosis or bradycardia), hypotension (mean blood pressure <35 mm-Hg), or bradycardia (heart rate <60/min) developed after use of either of the drugs. Once the baby was seizure-free for 5 days, anticonvulsants were stopped in the same order as they were started, and maintenance therapy was continued with the drug to which the case belonged.

IV PB and LEV were changed to oral once the baby was on 50% of enteral feeds. PB and LEV in respective group were stopped last at discharge if neurological examination was normal, and EEG demonstrated no electrical seizures. If neurological examination or EEG was abnormal or not done, then the drugs were continued after discharge, and baby was re-evaluated at the age of 3, 6, and 12 months for anticonvulsant efficacy, neurodevelopmental outcome, and other complications.

The primary outcome variable was cessation of clinical seizure activity (no seizure for 5 days). Secondary outcome variables were time taken to control seizures, survival at discharge, short-term adverse effect and long-term neurodevelopmental outcome at 12 months (Amiel-Tison method), and EEG control of seizures.

A neurological examination was done in all babies at discharge. It included an examination of overall activity, response to stimuli, ability to suck and swallow, active and passive tone of neck and trunk muscles and neonatal reflexes. Examination at 3, 6, and 12 months was done by examination of muscle tone by Amiel-Tison method (adductor angle, popliteal angle, dorsiflexion angle, and scarf sign) and evaluation of developmental retardation by Pathak adaptation of Bayley scale. Achievement of milestones such as social smile, recognition of mother, neonatal reflexes (Moro's reflex and grasp reflex), head circumference, and persistence of seizure was evaluated.

For those babies who could not come for follow-up, telephonic interviews of parents and local practitioners were conducted. They were asked about age, specific developmental milestones, weight gain, feeding, persistence of seizures, and overall perception of parents about neurological status and development. The neuromotor outcome was considered abnormal if tone of baby was outside of Amiel-Tison score range. Mental retardation was considered when Pathak adaptation of Bayley Scale came out to be abnormal.

Statistical analysis was done using intention to treat analysis. Results were analyzed using SPSS 23 software. Continuous data with normal distribution were analyzed by student *t*-test and non-normally distributed data by Mann–Whitney test. Categorical data were analyzed by Chi-square test or Fischer exact test, where applicable. Statistical data were expressed in mean and standard deviation. $p<0.05$ was considered significant.

RESULTS

Out of 80 neonates who were screened, 42 babies were randomized to LEV group and 38 babies were randomized to PB group. Baseline characteristics and seizures characteristics were comparable in both groups (Table 1). In case of multiple types of

seizures in a baby, he was classified on the basis of first seizure type only.

Cessation of clinical seizure was observed in 28 of the 42 (66.6%) neonates who received LEV and 31 of 38 (81.5%) neonates receiving PB first (p>0.05). After the maximum dose of PB, seizures were controlled in 32/38 (84.2%) in PB (p>0.05). Babies in whom seizure control were not achieved with first drug, after cross-over, seizure control was achieved in 40/42 (95.2%) of the neonates assigned to receive LEV first and 37/38 (97.3%) of those assigned to receive PB first (p>0.05).

Median (range) time taken to control all seizures was 30 min (10 min–48 h) in HIE Stage II, 60 min (10 min–6 d) in HIE Stage III, 52 min (15 min–24 h) in meningitis, and 11 h (30 min–3 h) in intracranial hemorrhage. There was no significant difference in seizure control in the two groups (p>0.05). Short-term adverse effects (cardiorespiratory depression and sedation) were noted in 3/42 babies in LEV group in comparison to 20/38 babies in PB group (p<0.05).

A total of 18 babies expired during NICU stay (ten babies in PB group and eight babies in LEV group, p>0.05), and 62 were discharged. Twelve of these 18 deaths were in babies with HIE Stage III. Of the remaining, four were in HIE Stage II, 1 had sepsis and 1 had intra-ventricular hemorrhage. None of these mortalities were within 4 h of giving drugs so likely to be unrelated to drugs used, but due to underlying condition.

Among 62 discharged babies, 14 were lost to follow-up, and 48 babies (25 babies in LEV group and 23 babies in PB group) were followed at 3 months, 6 months, and 12 months. Short- and long-term effect comparison between two groups is described in Table 2. After clinical control of seizures, EEG was done in 54 babies out of which 49 (90.7%) had normal EEG record and 5 (9.2%) had abnormal EEG records. There was no significant difference in incidence of abnormal EEG records in the two groups. The common abnormalities noted were electrical spikes and background abnormalities such as "burst suppression" pattern or low electrical voltage.

Table 1: Baseline characteristics of the study population

Parameters	LEV group (n=42) (%)	PB group (n=38) (%)
Gestational age* (week)	38.6 (1.45)	38.9 (1.87)
Weight* (kg)	2.71 (0.4)	2.55 (0.05)
Male sex	28 (66.6)	29 (76.3)
Etiology of seizure		
Hypoxic ischemic encephalopathy	23 (54.7)	20 (52.6)
Sepsis	18 (42.8)	16 (42.1)
Intracranial bleeding	1 (2.38)	2 (5.26)
Type of seizure		
Subtle	21 (50.0)	20 (52.6)
Tonic	18 (42.8)	16 (42.1)
Clonic	3 (7.14)	2 (5.26)

In number (%), *mean standard deviation, PB: Phenobarbitone, LEV: Levetiracetam

Table 2: Short- and long-term effect comparison between two groups

Outcome	LEV group	PB group	p-value
Short-term adverse effects			
Respiratory depression	1 (n=42)	7 (n=38)	0.024
Sedation	1 (n=42)	6 (n=38)	0.049
Hypotension	1 (n=42)	7 (n=38)	0.024
Long-term outcome at 12 months			
Neuromotor developmental delay	2 (n=25)	8 (n=23)	0.033
Mental retardation	1 (n=25)	6 (n=23)	0.044
Comorbidities	1 (n=25)	6 (n=23)	0.044

PB: Phenobarbitone, LEV: Levetiracetam

DISCUSSION

Our study demonstrated that LEV and PB, both were equally effective in the control of clinical seizures in term neonates irrespective of the etiology, but LEV is superior in terms of short-term adverse effect and long-term neurodevelopmental outcome than PB. The most common anticonvulsant used initially in neonates is PB [15]; although there are many concerns regarding the short-term as well as long-term adverse effects of PB. IV phenytoin and benzodiazepines are commonly employed as second-line IV medications in the treatment of NS [16]. In comparison, LEV is equally effective in controlling seizure and is safe due to its linear pharmacokinetics (half-life of 7 h), [17] rapid absorption (30 min), non-hepatic elimination, lack of protein binding (< 10%), and no known interactions with other anti-epileptic drugs [18].

Khan *et al.* studied 22 neonates on treatment with LEV and showed that seizures control in the majority (86%) of neonates was achieved by 1 h while all the patients were seizure-free by 72 h. No significant side effects were reported by them [19]. Abend *et al.* retrospectively studied 23 neonates with seizures who received LEV and observed 50% seizure reduction within 24 h. LEV was associated with >50% seizure reduction in 35% neonates, including seizure termination in 30% cases [20]. Shoemaker and Rotenberg reported seizure control with LEV. They did not report any adverse effects, and these babies remained seizure-free thereafter [21].

Ramantani *et al.* studied 38 neonates with seizures treated with LEV and reported that it is safe and effective in controlling NS [22]. Various studies have reported a wide range for LEV dosage ranging from 10 to 80 mg/kg/day [19-22]. Merhar *et al.* studied the pharmacokinetics of LEV in neonates and noted that neonates had lower plasma clearance, higher volume of distribution, and longer half-life as compared with older children and adults [23]. Falsaperla *et al*. conducted a study in 16 neonates with NS and used LEV as the lone drug and PB as adjunctive therapy and found it to be safe and effective first-line drug [24].

Maitre *et al*. compared 280 infants at 24 months corrected age and found that PB was associated with the worse neurodevelopmental outcomes than LEV [25]. Venkatesan *et al*. conducted a study on 127 neonates suffering from HIE and found LEV as an efficacious medication with no negative side effects [26]. It is one of the few studies done which compares the

effects of LEV with PB in NSs. However, double-blind prospective controlled studies and long-term evaluation of cognitive outcome is called for, to establish it as a reasonable alternative to PB. Lack of blinding of clinical outcomes, inability to monitor serum drug level and cerebral function, small sample size, and unavailability of bedside EEG were the limitation of our study.

CONCLUSION

The results obtained in our study illustrate the efficacy and safety of LEV as the first-line treatment in NSs. Our study demonstrated that LEV and PB, both were equally effective in control of clinical seizures in term neonates irrespective of the etiology; however, LEV was superior in terms of short-term adverse effects and long-term neurodevelopmental outcome than PB.

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